

Amendments to the Specification:

Please replace the paragraph beginning on page 7, line 12 of the specification with the following replacement paragraph.

Fig. 10: Lymphocyte Proliferation Assay on spleen cells from AN1792-treated (Fig. 10A)(~~upper panel~~) or PBS-treated (Fig. 10B)(~~lower panel~~).

Please replace the paragraph on page 7, beginning on line 27 with the following replacement paragraph.

Figs. 15(A-E)~~A-E~~: A β levels in the cortex of 12-month old PDAPP mice treated with AN1792 or AN1528 in combination with different adjuvants. The A β level for individual mice in each treatment group, and the median, mean, and p values for each treatment group are shown.

After the paragraph beginning on page 7, line 27, please add the following five new paragraphs.

Fig. 15A: The values for mice in the PBS-treated control group and the untreated control group.

Fig. 15B: The values for mice in the AN1528/alum and AN1528/MPL-treatment groups.

Fig. 15C: The values for mice in the AN1528/QS21 and AN1792/Freund's adjuvant treatment groups.

Fig. 15D: The values for mice in the AN1792/Thimerosal and AN1792/alum treatment groups.

Fig. 15E: The values for mice in the AN1792/MPL and AN1792/QS21 treatment groups.

Please replace the paragraph beginning at page 14, line 13 with the following replacement paragraph:

H₂N-Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala-OH (SEQ ID NO:42).

Please replace the paragraph beginning at page 16, line 16 with the following replacement paragraph:

In a further variation, an immunogenic peptide, such as a fragment of A β , can be presented by a virus or a bacteria as part of an immunogenic composition. A nucleic acid encoding the immunogenic peptide is incorporated into a genome or episome of the virus or bacteria. Optionally, the nucleic acid is incorporated in such a manner that the immunogenic peptide is expressed as a secreted protein or as a fusion protein with an outer surface protein of a virus or a transmembrane protein of a bacteria so that the peptide is displayed. Viruses or bacteria used in such methods should be nonpathogenic or attenuated. Suitable viruses include adenovirus, HSV, Venezuelan equine encephalitis virus and other alpha viruses, vesicular stomatitis virus, and other rhabdo viruses, vaccinia and fowl pox. Suitable bacteria include ~~Salmonella~~Salmonella and ~~Shigella~~Shigella. Fusion of an immunogenic peptide to HBsAg of HBV is particularly suitable. Therapeutic agents also include peptides and other compounds that do not necessarily have a significant amino acid sequence similarity with A β but nevertheless serve as mimetics of A β and induce a similar immune response. For example, any peptides and proteins forming β -pleated sheets can be screened for suitability. Anti-idiotypic antibodies against monoclonal antibodies to A β or other amyloidogenic peptides can also be used. Such anti-Id antibodies mimic the antigen and generate an immune response to it (*see Essential Immunology* (Roit ed., Blackwell Scientific Publications, Palo Alto, 6th ed.), p. 181). Agents other than A β peptides should induce an immunogenic response against one or more of the preferred segments of A β listed above (e.g., 1-10, 1-7, 1-3, and 3-7). Preferably, such agents

induce an immunogenic response that is specifically directed to one of these segments without being directed to other segments of A β .

Please replace the paragraph beginning at page 28, line 14, with the following replacement paragraph:

Some agents for inducing an immune response contain the appropriate epitope for inducing an immune response against amyloid deposits but are too small to be immunogenic. In this situation, a peptide immunogen can be linked to a suitable carrier to help elicit an immune response. Suitable carriers include serum albumins, keyhole limpet hemocyanin, immunoglobulin molecules, thyroglobulin, ovalbumin, tetanus toxoid, or a toxoid from other pathogenic bacteria, such as diphtheria, *E. coli*, cholera, or *H. pylori*, or an attenuated toxin derivative. Other carriers include T-cell epitopes that bind to multiple MHC alleles, e.g., at least 75% of all human MHC alleles. Such carriers are sometimes known in the art as “universal T-cell epitopes.” Examples of universal T-cell epitopes include:

Influenza Hemagglutinin: HA₃₀₇₋₃₁₉ PKYVKQNTLKLAT (SEQ ID NO:43)

PADRE (common residues bolded) AKXVAAWTLKAAA (SEQ ID NO:44)

Malaria CS: T3 epitope EKKIAKMEKASSVFNV (SEQ ID NO:45)

Hepatitis B surface antigen: HBsAg₁₉₋₂₈ FLLTRILTI (SEQ ID NO:46)

Heat Shock Protein 65: hsp65₁₅₃₋₁₇₁ DQSIGDLIAEAMDKVGNEG (SEQ ID NO:47)

bacille Calmette-Guerin QVHFQPLPPAVVKL (SEQ ID NO:48)

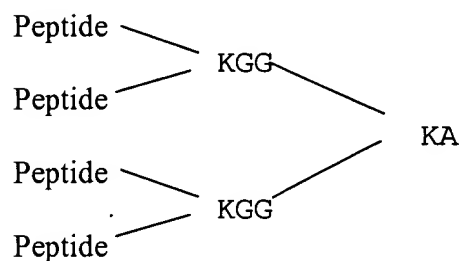
Tetanus toxoid: TT₈₃₀₋₈₄₄ QYIKANSKFIGITEL (SEQ ID NO:49)

Tetanus toxoid: TT₉₄₇₋₉₆₇ FNNFTVSFWLRVPKVSASHLE (SEQ ID NO:50)

HIV gp120 T1: KQIINMWQEVGKAMYA (SEQ ID NO:51).

Please replace the paragraph beginning at page 30, line 24 with the following replacement paragraph:

The MAP4 configuration is shown below, where branched structures are produced by initiating peptide synthesis at both the N terminal and side chain amines of lysine. Depending upon the number of times lysine is incorporated into the sequence and allowed to branch, the resulting structure will present multiple N termini. In this example, four identical N termini have been produced on the branched lysine-containing core. Such multiplicity greatly enhances the responsiveness of cognate B cells.



AN90549 (A β 1-7/Tetanus toxoid 830-844 in a MAP4 configuration):

DAEFRHDAQYIKANSKFIGITEL (SEQ ID NO:52)

AN90550 (A β 1-7/Tetanus toxoid 947-967 in a MAP4 configuration):

DAEFRHDFNNFTVSFWLRVPKVSASHLE (SEQ ID NO:53)

AN90542 (A β 1-7/Tetanus toxoid 830-844 + 947-967 in a linear configuration):

DAEFRHDAQYIKANSKFIGITELFNNFTVSFWLRVPKVSASHLE (SEQ ID NO:54)

AN90576: (A β 3-9)/Tetanus toxoid 830-844 in a MAP4 configuration):

EFRHDSGQYIKANSKFIGITEL (SEQ ID NO:55)

Peptide described in US 5,736,142 (all in linear configurations):

AN90562 (A β 1-7/ peptide) AKXVAAWTLKAAADAEFRHD (SEQ ID NO:56)

AN90543 (A β 1-7 x 3/ peptide):

DAEFRHDDAEFRHDDAEFRHDAKXVAAWTLKAAA (SEQ ID NO:57)

Other examples of fusion proteins (immunogenic epitope of A β bolded) include
AKXVAAWTLKAAA-DAEFRHD-DAEFRHD-DAEFRHD (SEQ ID NO:58)

DAEFRHD-AKXVAAWTLKAAA (SEQ ID NO:59)

DAEFRHD-ISQAVHAAHAEINEAGR (SEQ ID NO:60)

FRHDSGY-ISQAVHAAHAEINEAGR (SEQ ID NO:61)

EFRHDSG-ISQAVHAAHAEINEAGR (SEQ ID NO:62)

PKYVKQNTLKLAT-DAEFRHD-DAEFRHD-DAEFRHD (SEQ ID NO:63)

DAEFRHD-PKYVKQNTLKLAT-DAEFRHD (SEQ ID NO:64)

DAEFRHD-DAEFRHD-DAEFRHD-PKYVKQNTLKLAT (SEQ ID NO:65)

DAEFRHD-DAEFRHD-PKYVKQNTLKLAT (SEQ ID NO:66)

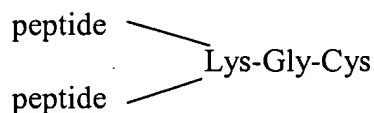
DAEFRHD-PKYVKQNTLKLAT-EKKIAKMEKASSVFNV-QYIKANSKFIGITEL-
FNNFTVSFWLRVPKVSASHLE-DAEFRHD (SEQ ID NO:67)

DAEFRHD-DAEFRHD-DAEFRHD-QYIKANSKFIGITEL-
FNNFTVSFWLRVPKVSASHLE (SEQ ID NO:68)

DAEFRHD-QYIKANSKFIGITELCFNNFTVSFWLRVPKVSASHLE (SEQ ID NO:69)

DAEFRHD-QYIKANSKFIGITELCFNNFTVSFWLRVPKVSASHLE-
DAEFRHD (SEQ ID NO:70)

DAEFRHD-QYIKANSKFIGITEL (SEQ ID NO:77) on a 2 branched resin



EQVTNVGGAISQAVHAAHAEINEAGR (SEQ ID NO:71) (Synuclein fusion protein in
MAP-4 configuration).

Please replace the paragraph beginning on page 46, line 21 with the following replacement paragraph:

The methods work by administering a reagent, such as antibody, that binds to A β ~~in the patient to the patient~~, and then detecting the agent after it has bound. Preferred antibodies bind to A β deposits in a patient without binding to full length APP polypeptide. Antibodies binding to an epitope of A β within amino acids 1-10 are particularly preferred. In some methods, the antibody binds to an epitope within amino acids 7-10 of A β . Such antibodies typically bind without inducing a substantial clearing response. In other methods, the antibody binds to an epitope within amino acids 1-7 of A β . Such antibodies typically bind and induce a clearing response to A β . However, the clearing response can be avoided by using antibody fragments lacking a full length constant region, such as Fabs. In some methods, the same antibody can serve as both a treatment and diagnostic reagent. In general, antibodies binding to epitopes C-terminal of residue 10 of A β ~~do not~~ of A β ~~do not~~ show as strong signal as antibodies binding to epitopes within residues 1-10, presumably because the C-terminal epitopes are inaccessible in amyloid deposits. Accordingly, such antibodies are less preferred.

Please replace the paragraph beginning at page 59, line 25 with the following replacement paragraph:

Spleens were removed from nine AN1792-immunized and 12 PBS-immunized 18-month old PDAPP mice 7 days after the ninth immunization. Splenocytes were isolated and cultured for 72 h in the presence of A β 40, A β 42, or A β 40-1 (reverse order protein). The mitogen Con A served as a positive control. Optimum responses were obtained with >1.7 μ M protein. Cells from all nine AN1792-treated animals proliferated in response to either A β 1-40 or A β 1-42 protein, with equal levels of incorporation for both proteins (Fig. 10A)(~~Fig. 10, Upper Panel~~). There was no response to the A β 40-1 reverse protein. Cells from control animals did not respond to any of the A β proteins (Fig. 10B)(~~Fig. 10, Lower Panel~~).

Please replace the paragraph beginning at page 60, line 24 with the following replacement paragraph:

Preparation of coupled A β peptides: four human A β peptide conjugates (amino acid residues 1-5, 1-12, 13-28, and 33-42, each conjugated to sheep anti-mouse IgG) were prepared by coupling through an artificial cysteine added to the A β peptide using the crosslinking reagent sulfo-EMCS. The A β peptide derivatives were synthesized with the following final amino acid sequences. In each case, the location of the inserted cysteine residue is indicated by underlining. The A β 13-28 peptide derivative also had two glycine residues added prior to the carboxyl terminal cysteine as indicated.

A β 1-12 peptide	NH ₂ -DAEFRHDSGYEVC- <u>COOH</u> (<u>SEQ ID NO:72</u>)
A β 1-5 peptide	NH ₂ -DAEFR <u>C</u> -COOH (<u>SEQ ID NO:73</u>)
A β 33-42 peptide	NH ₂ - <u>C</u> -amino-heptanoic acid-GLMVGGVVIA-COOH (<u>SEQ ID NO:74</u>)
A β 13-28 peptide	Ac-NH-HHQLVFFAEDVGSNKG <u>GC</u> -COOH (<u>SEQ ID NO:75</u>)

Please replace the paragraph beginning at page 62, line 12 with the following replacement paragraph:

Preparation of the pBx6 protein: An expression plasmid encoding pBx6, a fusion protein consisting of the 100-amino acid bacteriophage MS-2 polymerase N-terminal leader sequence followed by amino acids 592-695 of APP (β APP) was constructed as described by Oltersdorf et al., J. Biol. Chem. 265, 4492-4497 (1990). The plasmid was transfected into ~~E.~~ *E. coli* and the protein was expressed after induction of the promoter. The bacteria were lysed in 8M urea and pBx6 was partially purified by preparative SDS PAGE. Fractions containing pBx6 were identified by Western blot using a rabbit anti-pBx6 polyclonal antibody, pooled, concentrated using an Amicon Centriprep tube and dialysed against PBS. The purity of the preparation, estimated by Coomassie Blue stained SDS PAGE, was approximately 5 to 10%.

Please replace the paragraph beginning on page 68, line 17 with the following replacement paragraph:

Groups of 7-9 month old PDAPP mice each are injected with 0.5 mg in PBS of polyclonal anti-A β or specific anti-A β monoclonals as shown below. The cell line designated RB44-10D5.19.21 producing the antibody 10D5 has the ATCC accession number PTA-5129, having been deposited on April 8, 2003. All antibody preparations are purified to have low endotoxin levels. Monoclonals can be prepared against a fragment by injecting the fragment or longer form of A β into a mouse, preparing hybridomas and screening the hybridomas for an antibody that specifically binds to a desired fragment of A β without binding to other nonoverlapping fragments of A β .

Please replace the paragraph beginning on page 76, line 17 with the following amended paragraph:

To prepare formulation doses with alum (Groups 1 and 5). A β peptide in PBS was added to Alhydrogel (two percent aqueous aluminum hydroxide gel, Sargeant, Inc., Clifton, NJ) to reach concentrations of 100 μ g A β ~~peptide per 1 mg of alum~~ peptide per 2 mg of alum. 10X PBS was added to a final dose volume of 200 ml in 1X PBS. The suspension was then gently mixed for approximately 4 hr at RT prior to injection.

Please replace the paragraph beginning at page 77, line 3 with the following amended paragraph:

To prepare formulation doses with Freund's Adjuvant (Group 4), 100 g of AN1792 in 200 l PBS was emulsified 1:1 (vol:vol) with Complete Freund's Adjuvant (CFA) in a final volume of 400 l for the first immunization. For subsequent immunizations, the antigen was similarly emulsified with Incomplete Freund's Adjuvant (IFA). For the formulations containing the adjuvants alum, MPL or QS21, 100 g per dose of AN1792 or AN1528 was combined with alum ~~(1 mg per dose)~~ (2 mg per dose) or MPL (50 g per dose) or QS21 (25 g per dose) in a final volume of 200 l PBS and delivered by subcutaneous inoculation on the back between the

shoulder blades. For the group receiving FA, 100 g of AN1792 was emulsified 1:1 (vol:vol) with Complete Freund's adjuvant (CFA) in a final volume of 400 l and delivered intraperitoneally for the first immunization, followed by a boost of the same amount of immunogen in Incomplete Freund's adjuvant (IFA) for the subsequent five doses. For the group receiving AN1792 without adjuvant, 10 g AN1792 was combined with 5 g thimerosal in a final volume of 50 l PBS and delivered subcutaneously. The ninth, control group received only 200 l PBS delivered subcutaneously. Immunizations were given on a biweekly schedule for the first three doses, then on a monthly schedule thereafter on days 0, 16, 28, 56, 85 and 112. Animals were bled six to seven days following each immunization starting after the second dose for the measurement of antibody titers. Animals were euthanized approximately one week after the final dose. Outcomes were measured by ELISA assay of β A and APP levels in brain and by immunohistochemical evaluation of the presence of amyloid plaques in brain sections. In addition, β -specific antibody titers, and β -dependent proliferative and cytokine responses were determined.

Please replace the paragraph beginning at page 80, line 1 with the following replacement paragraph:

The results of AN1792 or AN1592 treatment with various adjuvants, or thimerosal on cortical amyloid burden in 12-month old mice determined by ELISA are shown in Figs. 15A-15E. In PBS control PDAPP mice (Fig. 15A), the median level of total A in the cortex at 12 months was 1,817 ng/g. Notably reduced levels of A were observed in mice treated with AN1792 plus CFA/IFA (Fig 15C), AN1792 plus alum (Fig 15D), AN1792 plus MPL (Fig 15E) and QS21 plus AN1792 (Fig 15E). The reduction reached statistical significance ($p < 0.05$) only for AN1792 plus CFA/IFA (Fig 15C). However, as shown in Examples I and III, the effects of immunization in reducing A levels become substantially greater in 15 month and 18 month old mice. Thus, it is expected that at least the AN1792 plus alum, AN1792 plus MPL and AN1792 plus QS21 compositions will achieve statistical significance in treatment of older mice. By contrast, the AN1792 plus the preservative thimerosal (Fig 15D) showed a median level of A about the same as that in the PBS treated mice. Similar results were obtained when cortical

levels of A β 42 were compared. The median level of A42 in PBS controls was 1624 ng/g. Notably reduced median levels of 403, 1149, 620 and 714 were observed in the mice treated with AN1792 plus CFA/IFA, AN1792 plus alum, AN1792 plus MPL and AN1792 plus QS21 respectively, with the reduction achieving statistical significance ($p=0.05$) for the AN1792 CFA/IFA treatment group. The median level in the AN1792 thimerosal treated mice was 1619 ng/g A42.

Please replace the paragraph beginning on page 83, line 14 with the following replacement paragraph:

Sixty male and female, heterozygous PDAPP transgenic mice, 8.5 to 10.5 months of age were obtained from Charles River Laboratory. The mice were sorted into six groups to be treated with various antibodies directed to A β . Animals were distributed to match the gender, age, parentage and source of the animals within the groups as closely as possible. As shown in Table 10, the antibodies included four murine A β -specific monoclonal antibodies, 2H3 (directed to A β residues 1-12), 10D5 (directed to A β residues 1-16) (details of the deposit of 10D5 are discussed in Example VI, *supra*), 266 (directed to A β residues 13-28 and binds to monomeric but not to aggregated AN1792), 21F12 (directed to A β residues 33-42). A fifth group was treated with an A β -specific polyclonal antibody fraction (raised by immunization with aggregated AN1792). The negative control group received the diluent, PBS, alone without antibody.

Please replace the paragraph beginning on page 102, line 8 with the following replacement paragraph:

The exact array of linear peptides recognized by the antibodies in the serum samples from animals immunized with AN1792 was determined by an ELISA that measured the binding of these antibodies to overlapping peptides that covered the entire A β 1-42 sequence. Biotinylated peptides with partial sequences of AN1792 were obtained from Chiron Technologies as 10 amino acid peptides with an overlap of 9 residues and a step of one residue per peptide (synthesis No. 5366, No. 5331 and No. 5814). The first 32 peptides (from the eight amino acid position upstream of the N-terminal of AN1792 down to the twenty-fourth amino acid of AN1792) are biotinylated on the C-terminal with a linker of GGK. The last 10 peptides

(repeating the thirty-second peptide from the previous series) are biotinylated on the N-terminal with a linker consisting of EGEG (SEQ ID NO:76). The lyophilized biotinylated peptides were dissolved at a concentration of 5 mM in DMSO. These peptide stocks were diluted to 5 μ M in TTBS (0.05% Tween 20, 25 mM Tris HCl, 137 mM NaCl, 5.1 mM KCl, pH=7.5). 100 μ l aliquots of this 5 μ M solution were added in duplicate to streptavidin pre-coated 96-well plates (Pierce). Plates were incubated for one hour at room temperature, then washed four times with TTBS. Serum samples were diluted in specimen diluent without azide to normalize titers, and 100 μ l was added per well. These plates were incubated one hour at room temperature and then washed four times with TTBS. HRP-conjugated goat anti-human antibody (Jackson ImmunoResearch) was diluted 1:10,000 in specimen diluent without azide and 100 μ l was added per well. The plates were again incubated and washed. To develop the color reaction, TMB (Pierce), was added at 100 μ l per well and incubated for 15 min prior to the addition of 30 μ l of 2 N H₂SO₄ to stop the reaction. The optical density was measured at 450 nm on a Vmax or Spectramax colorimetric plate reader.

Please replace the paragraph beginning on page 107, line 26 with the following replacement paragraph:

The brain homogenates were diluted 1:10 with ice cold Casein Diluent (0.25% casein, PBS, 0.05% sodium azide, 20 μ g/ml aprotinin, 5 mM EDTA pH 8.0, 10 μ g/ml leupeptin) and then centrifuged at 16,000 x g for 20 min at 4 C. The synthetic A β protein standards (1-42 amino acids) and the APP standards were prepared to include 0.5 M guanidine and 0.1% bovine serum albumin (BSA) in the final composition. The "total" A β sandwich ELISA utilizes monoclonal antibody (mAb) 266, specific for amino acids 13-28 of A β (Seubert, et al.), as the capture antibody, and biotinylated mAb 3D6, specific for amino acids 1-5 of A β (Johnson-Wood, et al), as the reporter antibody. The 3D6 mAb does not recognize secreted APP or full-length APP, but detects only A β species with an amino-terminal aspartic acid. The cell line producing the antibody 3D6 has the ATCC accession number PTA-5130, having been deposited on April 8, 2003. This assay has a lower limit of sensitivity of ~50 ng/ml (11 nM) and shows no cross-

Application No. 09/724,940
First Preliminary Amendment Filed November 25, 2003

reactivity to the endogenous murine A β protein at concentrations up to 1 ng/ml (Johnson-Wood et al., *supra*).

Amendments to the Drawings:

The first attached replacement drawing sheet (Figs. 1 and 2) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters.

The second attached replacement drawing sheet (Figs. 3 and 4) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters. Figure 4 has been further amended to replace "retrospelenial" with "retrospleniai."

The third attached replacement drawing sheet (Figs. 5 and 6) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters.

The fourth attached replacement drawing sheet (Figs. 7 and 8) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters.

The fifth attached replacement drawing sheet (Fig. 9) has been amended to replace "retroslpenial" with "retrospleniai."

The sixth attached replacement drawing sheet (Fig. 10) has been amended identify the upper and lower panels of Figure 10 as Figure 10A and 10B, respectively. Figure 10 has also been amended to replace " retroslpenial" with "retrospleniai."

The seventh attached replacement drawing sheet (Figs 11 and 12) includes Fig. 11 which has been amended to include a legend.

The eighth attached replacement drawing sheet (Figs. 13 and 14) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters.

The ninth attached replacement drawing sheet (Fig. 15A) has been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Support this amendment is provided by the informal Figure 15 as originally filed in U.S. Application No. 09/201,430, filed November 30, 1998, which is incorporated by reference into the instant application.

The tenth attached replacement drawing sheet (Fig. 15B) has been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Support this amendment is provided by the informal Figure 15 as originally filed in U.S. Application No.

09/201,430, filed November 30, 1998, which is incorporated by reference into the instant application.

The eleventh attached replacement drawing sheet (Fig. 15C) has been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Support this amendment is provided by the informal Figure 15 as originally filed in U.S. Application No. 09/201,430, filed November 30, 1998, which is incorporated by reference into the instant application.

The twelfth attached replacement drawing sheet (Fig. 15D) has been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Figure 15D has been further amended to replace "2 μ g/ml alum" with "2 mg/ml alum." Support for these amendments is provided by the informal Figure 15 as originally filed in U.S. Application No. 09/201,430, filed November 30, 1998, which is incorporated by reference into the instant application.

The thirteenth attached replacement drawing sheet (Fig. 15E) has been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Support this amendment is provided by the informal Figure 15 as originally filed in U.S. Application No. 09/201,430, filed November 30, 1998, which is incorporated by reference into the instant application.

The fourteenth attached replacement drawing sheet (Fig. 16) has been amended to orient the words in a left-to-right fashion when the page is turned so that the top becomes the left side. Figure 16 has been further amended to replace "Anti AB" with "Anti-Abeta." Support for this amendment can be found on page 92, lines 25-33 of the specification.

The fifteenth replacement drawing sheet (Fig. 17) has been amended to orient the words in a left-to-right fashion when the page is turned so that the top becomes the left side.

The sixteenth attached replacement drawing sheet (Fig. 18) has been amended to orient the words in a left-to-right fashion when the page is turned so that the top becomes the left side.

The seventeenth attached replacement drawing sheet (Fig. 19) been amended to delete one of the occurrences of the sequence "VGSNKGAIIG."

Application No. 09/724,940
First Preliminary Amendment Filed November 25, 2003

The eighteenth attached replacement drawing sheet (Fig. 20) been amended to delete one of the occurrences of the sequence "VGSNKGAIIG."

18 replacement drawing sheets are submitted herewith.